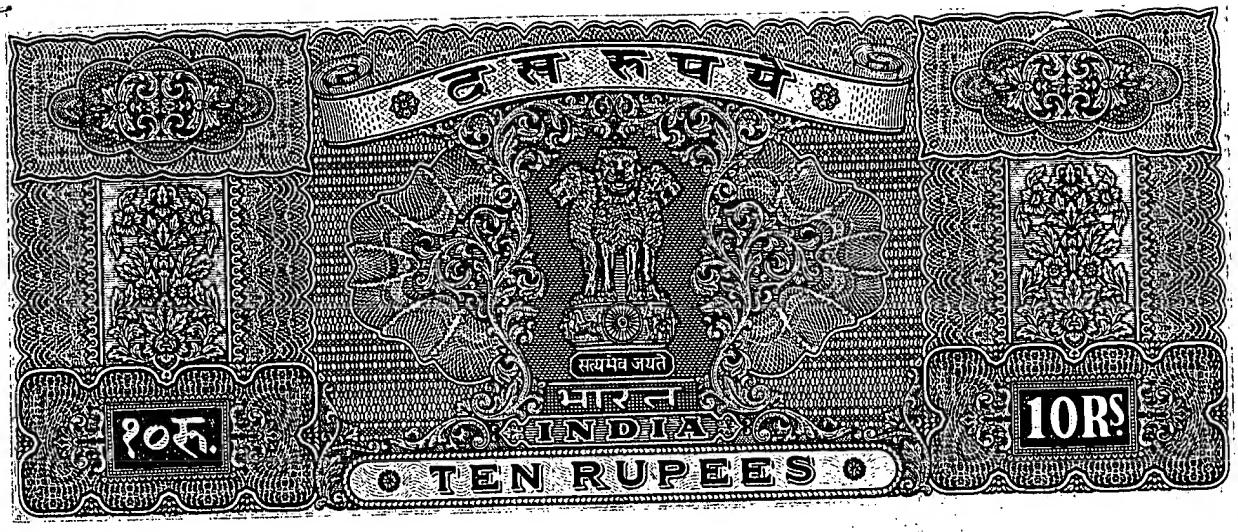

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Sahni et al.	Group Art Unit: 1652
Serial No.: 09/940,235	Examiner: Sheridan L. Swope
Filed: 27th August 2001	
For: Novel clot-specific streptokinase proteins possessing altered plasminogen activation characteristics and a process for the preparation of said proteins	Attorney Docket No: 07064-009002

To,
The Assistant Commissioner for Patents
Washington, D.C. 20231

Declaration Under 37 C.F.R. § 1.132

I, Girish Sahni age 47 years, residing at Chandigarh, INDIA, and a citizen of India, do hereby state as under.

I am a Scientist at the Institute of Microbial Technology, sector 39-A, Chandigarh-160036, India. I graduated in the year 1976 from Panjab University located at Chandigarh, INDIA. I completed my Master's Degree in Microbiology from Panjab University at Chandigarh, INDIA in the year 1978. Subsequently, I completed my doctoral degree in Biochemistry from the Indian Institute of Science, Bangalore, India in the year 1984.

Sr. N 44441 Date 28/11/03

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Claims

1. A genetically engineered hybrid polypeptide plasminogen activator, wherein said activator comprises a streptokinase (SK) or its functional component containing essentially polypeptide fragment corresponding to residues 16-383 of SK, whereby retaining upto 100% plasminogen activity, and finger-type fibrin binding domain (FBD) pairs of 1-2 and/or 4-5 of fibronectin or its functional components, bound specifically to N and/or C terminals of the SK, with the said activator showing a desired time-lag in plasminogen activation due to a plasmin-dependent activation mechanism.

2. Deleted

3. An activator as claimed in claim 1, wherein the time lag is ranging between 5 to 30 minutes.

32. A pharmaceutical composition comprising a genetically engineered hybrid polypeptide plasminogen activator of claim 1, and stabilizer(s).

After completing my doctoral degree, I took up my first assignment as a post-doctoral scientist with the University of California, Santa Barbara, USA in the year 1984. After that, I joined the Rockefeller University, New York as senior research associate, and as Adjunct Faculty in 1986. Subsequently, in 1991, I joined as a senior faculty member at the Institute of Microbial Technology (IMTECH), Chandigarh, a constituent institution of the Council of Scientific and Industrial Research, India, where I am continuing to now work on molecular biology of proteins for the last twelve years. Presently, I am working as the Deputy Director of this institute (since 2001).

One of the projects undertaken by IMTECH, Chandigarh, INDIA is "*Novel clot-specific streptokinase proteins possessing altered plasminogen activation characteristics and a process for the preparation of said proteins*". This project was undertaken in the year 1992. The scientists involved in the study were myself, Rajesh Kumar, Chaiti Roy, Kammara Rajogopal, Deepak Nihalani, Vasudha Sundaram, and Mahavir Yadav. I am the main scientist (project leader) in this study. I am aware of US patent application No. 09/940,235 filed in respect of this project. I am also aware and familiar with all the office actions, objections of the Examiner and the references cited by the Examiner. Therefore, I am completely and fully aware of all the facts relating to this project as well as the present patent application.

I wish to state at the outset that the challenge in the objective set out by the inventors was not just to make a "carrier SK" of FBDs but, in addition, to make a carrier (hybrid protein) that would become active in a clot-specific manner and NOT merely to make fusions between SK and FBDs with PG activation characteristics indistinguishable from normal SK which activates PG immediately without any lag i.e. virtually immediately on contact between the two.

In contrast, the design principles in applicants' constructs are such that the disclosed constructs are **initially inactive** due to the fusions, **but get activated by plasmin in the blood clot after the 'inhibiting' FBDs are cleaved off.** Unlike these, natural SK is not dependent on plasmin activation (since it is 'self-activated') and thus begins to activate PG *throughout the circulation immediately after injection.* Clearly, ours' was a far more complex and intricate objective than merely making a FBD-SK fusion, such as that claimed by Malke et al. or Brown et al. since it required a "molecular switch" that would allow slow activation either through a conformational change or proteolytic scission mechanism *specific* to the target blood clot, or 'sense' a substance in the target blood clot that acts as a trigger for its (local) activation.

Thus, the basic approach of the inventors was totally distinct from that of the cited arts. *The authors of the cited arts have limited their focus on fibrin binding.* The cited arts are not focusing upon the fact that the activity of the SK will be expressed en route to the fibrin clot located at the site of occlusion, and this systemic activation will affect various protein molecules present in the bloodstream other than fibrin, thereby producing serious deleterious side-effects in the body, such as hemorrhage and destruction of blood factors, an issue that is well documented in the scientific literature. However, the genetically modified recombinant SK designed in our patent will be inactive till it reaches the site of action. There, because it is activated by plasmin (unlike natural SK) and since plasmin is an integral component of blood clots, the activation will be localized, quite unlike normal SK. It may be mentioned here that in the free circulation, plasmin is immediately inactivated by inhibitors but remains active within blood clots due to a 'shielding' effect of the blood clot matrix.

Also, it is important to note that all protein fusions will not automatically work, unless made the 'right' way that preserves initial bio-activity of the participating partners (see: Alcala P, Ferrer-Miralles N and Villaverde A., 2003, FEBS Lett vol. 533: 115; Fort CF, Souminen I and Glatz CE., 1991 Prot. Expression and Purif. Vol. 2: 95). In applicants' case, the objective was not only to preserve original function/s (i.e. of SK and the FBDs) but **also to introduce an altogether new property** viz. delayed PG activation through plasmin-mediated scission of the FBDs, a task made even more difficult by the fact that preservation of original native activity in any two fusion partners, and 'facilitated' cleavage of a given fusion protein with a protease, is usually not a straightforward and predictable process (Marshall SA, Lazar GA, Chirino AJ and Desjarlais JR., 2003, Drug Discovery Today vol. 8: 212; Jenny RJ, Man KG and Lundblad RL., 2003, Prot. Expression and Purif. Vol 31: 1-11).

Fibronectin domains are structurally and functionally distinct from human plasminogen kringle domains, and our fusions, unlike that taught by Malke et al, have plasminogen (PG) activation characteristics that show an initial time lag of several (5-30) minutes' duration unlike natural, un-engineered streptokinase (SK), which activates PG on contact (i.e. almost instantaneously) leading to severe side-effects. Hence, this *deliberately* engineered property is a much coveted characteristics in an improved thrombolytic drug since it allows the agent to home onto its target (pathological blood clot) without activating the plasminogen systemically throughout the circulation. **Malke et al never even perceived the concept of deactivating and subsequently, activating the recombinant SK. Further, they make absolutely no reference to the fact that the deactivation and then reactivation could offer such a significant benefit in this important field of medical sciences, leave alone actually demonstrating this property.**

It is well-established that after injection into the blood, SK makes a tight 1:1 stoichiometric complex with the plasminogen present in the blood stream. It is this two-molecule complex that is the active proteolytic, plasminogen-activating principle or enzyme, that, in fact is the effective therapeutic molecule (reviewed in Castellino, FJ ,1981, Chemical reviews vol. 81:431). This SK-PG complex rapidly self-activates to SK-plasmin (in which the zymogen, plasminogen has been converted to its proteolytically active form -- plasmin, by an intramolecularly initiated process whose mechanistic details are not yet fully understood); the SK-plasmin complex then further acts (as an enzyme) on un-complexed, circulating substrate PG molecules to convert these into freely circulating plasmin, which dissolves the pathological blood clots in the vascular system as they travel throughout the bloodstream. **However, the chief problem with this scenario is that the plasmin destroys several other vitally required blood factors as well, briefly alluded to above, often leading to severe side-effects, including uncontrolled internal bleeding.**

Hence, it was important to design SK derivatives with minimal side effects and high target specificity i.e. localized action in the vicinity of the blood clot and *not throughout the system.* For this purpose, applicants have designed, produced and characterized new forms of SK that do not get activated immediately but only do so after a distinct time-delay. This property has neither been anticipated nor been shown by Malke et al.

In our patent application, we disclose not only the specific molecular designs that confer the PG activation time-lag property, but also provide a scientific rationale for this phenomenon *viz.* that the initial time-lag observed is actually due to a plasmin-dependent mechanism operative in these new forms (as opposed to the well-known observation that activation of the natural SK-PG activator complex is *independent* of the presence of Plasmin i.e. the zymogen, PG, in the activator complex is activated through an autocatalytic process (see: Castellino, 1981, Chem. Reviews vol. 81: 431-442).

The plasmin-dependence of PG activation by the hybrids disclosed in our application is established in Example 8, paragraph 2, of our patent specifications, wherein it is shown that as a result of deliberate depletion of residual plasmin in the PG preparation used in the experiment by pre-adsorption to a specific, plasmin-absorbing affinity material (soybean trypsin inhibitor-agarose) the *in vitro* lag increased significantly showing that the removal/diminution of plasmin in the PG preparation to be activated resulted in abolishment/decrease in lag, and conversely, it significantly decreased upon increasing the plasmin concentration in substrate PG. Further, the activation of PG by the hybrids, and concomitant abolishment of the lag, was found to coincide with the cleavage of the fused fibrin binding domains from the SK portion of the hybrid (Example 8). These observations **clearly established that the molecular mechanism of the observed lag is steric hindrance by the fused FBDs, and their scission from the SK component by plasmin-mediated proteolysis results in the abolishment of**

the lag. Thus, unlike native SK which forms an activator enzyme with the zymogen (PG) almost instantaneously, the new forms require the presence of plasmin to activate substrate. **And since free plasmin is absent in the circulation normally, but present in the blood clots, the activators with such a property, together with strong fibrin affinity, are indisputably improved in terms of their therapeutic properties related to improved localized activation. The presence of these two properties simultaneously in our constructs, and the unique mechanism associated with these, is clearly distinct both from Malke et al's and Brown et al's constructs.**

To reiterate, since the pathological "target" clot is relatively plasmin-rich, it would allow the *in situ* activation of the modified SK molecules ones they home into the clot by virtue of their fibrin affinity. *More importantly, since free plasmin is rare or absent in circulation, the constructs would remain in an inactive state while sojourning the circulating system until their absorption to the clot.*

The Brown et al patent teaches the preparation of chemically cross-linked molecules between SK and FBD. The linkages of this nature results in cross-linked polypeptides with chemically undefined make-up since the hetero-bi-functional cross-linking can potentially take place between any of the several amino acid residue side-chains in the two proteins. Further, none of the introduced cross-links were defined with respect to their location in either of the participating polypeptide segment.

Thus, the specifics of the designing of constructs in Brown et al. essentially remain chemically uncharacterized. This situation is fundamentally different when chimeric molecules are produced utilizing rDNA technology since the hybrid produced is a *contiguous* polypeptide (a fusion peptide) wherein both participants or domains in the hybrids are linked to each other *via* a polypeptide bond whose location is *unambiguously* defined. It is also important that the fusion of one domain with another can potentially occur in a number of configurations e.g., either at the N-terminus or C-terminus of the "acceptor" protein (in this case, SK), or within the "body" of the acceptor protein in an "in-frame" manner, or at both termini together. **However, which configuration would show the desired "functional" effect cannot often be predicted *a priori.* Nevertheless, since the introduction of a desired attribute into a hybrid protein is a critical feature of the selected design(s), it can not obviously be left to chance or expectation alone and the desired property(ies) ought to be clearly demonstrated in the resultant construct. In applicants' specifications, the configurations, exact locations and nature of the fusion junctions etc in hybrids that show the desired attributes have been clearly defined. In the case of Brown et al, however, a population of differently cross-linked conformers/isomers of hybrids were formed, and the correlation of activity and structure becomes questionable since a statistical average of the functional behaviour of the heterogeneous population was examined. In Malke et al's case, the desired property is also non-existent.**

None of the cited arts makes even a vague reference to the role of plasmin present in the vicinity of the fibrin to play a critical role in the activation of the genetically modified recombinant SK. Further, the examiner must appreciate that **plasmin can act upon the biological molecule of the instant application developed by recombination technique. However, it just cannot work on a SK-fibronectin conjugate developed by chemical binding.**

We have actually checked this after preparing a SK-FBD conjugate using Brown et al's methodology and find no effect of plasmin on PG activation kinetics, nor a time-delayed mode of PG activation. In case of Malke et al's constructs also, such an effect could not be seen in actual experimentation by us. It is highly probable that this is so because the kringle domains (unlike the FBDs, fused in our constructs), despite being joined at the N-terminus of SK, do not produce the required hindrance to plasmin-mediated proteolysis that the fibronectin FBDs do, and are likely immediately cleaved off, without generating any lag in PG activation kinetics, a fact that is also reported by Malke et al themselves in their patent. Hence, it is unjustified to assume that simply by looking at Malke et al on the one hand, and at Brown et al, on the other, it would become obvious to carry out what the inventors have done. Though there should not be any hindsight reading and even if there is a hindsight reading, a person skilled in the art would not be able to arrive at the invention by combing the cited arts.

The altered mechanism of PG activation displayed by the hybrids in our application has powerful implications in their therapeutic applications since free plasmin is rarely present in the circulation as it is rapidly cleared by circulating plasma proteins called Serpins, such as alpha-2 macroglobulin and/or alpha-2 antiplasmin. References in this context may be made to: Gonias, Einarsson and Pizzo, 1982, J. Clin. Invest. vol. 70, 412-423; Rajagopalan, Gonias and Pizzo, 1987, J. Biol. Chem. vol. 262, 3660-3669). Since free plasmin is relatively abundant in the pathological clot due to local activation of the PG bound to the thrombus by the small quantities of intrinsic TPA (Colman, Hirsh, Marder and Salzman [eds]., 1994, Haemostasis and thrombosis, Basic Principles and Clinical Practice., J. B. Lipincott Co., Philadelphia) it allows the *in situ* activation of the modified SK molecules once they home onto the clot by virtue of their strong fibrin affinity. In other words, since free plasmin is rare or absent in circulation, the constructs would remain in an inactive state while sojourning the circulatory system until their absorption to the clot.

Since it takes a few minutes for a molecule to circulate in the body *via* the main blood vessels, the ability to remain transiently inactive (unlike natural SK) until the protein reaches the pathological blood clot wherein it gets activated locally for reasons stated above, unambiguously translates into an advantageous therapeutic property, namely to activate PG predominantly in the vicinity of the target

without systemic PG activation in the overall circulatory system, unlike a PG activator that activates PG as soon as it is introduced into the circulatory system.

Further, by virtue of the elements of design employed in the engineering of an initial PG activation time lag -- a vital component of our construct – our recombinant plasminogen activator is clearly distinguishable from that of Malke et al. which discloses a fusion of plasminogen kringle domains at the N-terminus of SK with no reported alteration in PG activation characteristics compared to native SK. In addition, our specification discloses designs that demonstrate different lag periods for PG activation, which underlies the fact that the modulation of the time lag is also a distinct feature of our invention, a property that is obviously of tremendous significance in designing and then choosing a tailor-made thrombolytic protein for different clinical scenarios.

In Applicants' specifications, the hybrid polypeptides contain fusions of SK and finger FBD domains that are juxtaposed with SK, or parts of SK sufficient for PG activation, in either a format wherein the different FBDs are either fused at the N-terminal side of SK (Fig. 1 in specification), or fused at the C-terminal end of SK, or fused at the N-terminal end *as well as* C-terminal end of SK simultaneously. In all cases, the detailed inter-genic/inter-domain linker regions, which are vital for the desired function viz. fibrin affinity and time-delayed PG activation in the hybrids, are described fully in individual Examples. It should be mentioned that, in general, **it is well recognized in the art that contiguous fusion of two proteins can be detrimental to the functioning of either or both partners. Proteins are folded into complex three-dimensional shapes, that govern their unique biological properties. Production of fusions between two proteins can disrupt the folding of the protein/s in gross as well as subtle ways. Moreover, access to, and of, ligands and substrates may also be irreversibly affected by fusions.** In the literature, examples abound where fusions between different proteins were found to compromise to one degree or another, the functioning of the two partners, although in some cases such fusions may allow some survival of function. Indeed, the manner in which the fusions are planned and designed, the role of the termini (both N- and C-) of each partner, the flexibilities of the respective termini and their interaction with neighboring regions in the folded partners, the relative importance of these regions in the biological functioning of the two proteins etc are factors that will govern whether a given fusion will "work". *A priori*, **therefore, it could not be predicted whether, in general, the fusion of the FBDs with SK would allow the functioning of SK to survive in the manner desired in our patent i.e. with a time-delayed function in terms of PG activation kinetics alongwith survival of fibrin affinity in the construct. Indeed, in the case of Malke et al, the fusion of the kringles at the N-terminus did not bring about any discernable change in the characteristics of the SK.**

This further establishes our observation that the time lag was neither an object nor result of any of the cited arts. Further, the fact that both the site and method of binding of finger FBD with the SK is *critical* for engendering the desired activities. Thus, the product of the cited arts cannot be assumed to inherently have the desired activities.

In addition, as explained/rationalized in our patent application's introduction (see section, 'Background of the invention', as well as the sections 'Field of the invention', and 'Advantages of the present invention'), the clot-specific streptokinases disclosed in our application possess not only enhanced fibrin affinity, but are so designed [particularly with respect to the amino acid sequences in and around the fusion junctions (e.g. see Examples 3-6), with the disclosed design/s being critical for introducing the properties mentioned] that the molecules activate plasminogen only after an initial lag wherein no or negligible PG activation occurs, unlike the case of natural SK, which activates PG on contact. As explained in the application, the ability to circulate in an inactive state in the body after injection would significantly retard the systemic/generalized PG activation observed with unmodified/natural SK therapy. **This capability for a plasmin-dependent lag in PG activation is a direct result of the design of the fusion construct and not merely an inherent proper of *any* fusion product between SK and *any* fibrinbinding domain.** Based on our research group's findings (Nihalani, D., Kumar, R. and Sahni, G. 1998, *Protein Science* vol. 7:637; see, particularly Fig. 8) we reasoned that since there are two main 'sensitive' regions in SK, one located at the N-terminal region and the other towards the C-terminus of the molecule that are chiefly involved in interacting with PG, we might be able to successfully design constructs that would probably exhibit the desired characteristics if the 'fusing partner' is able to sterically inhibit the functioning of these two PG interacting regions in SK. Thus, as a direct result of these finding, we reasoned that fusion of *appropriate* FBDs either at the N- or C-terminus (or both, simultaneously) would hinder or retard the PG activation process to varying extents. However, in order to ensure that such a hindrance was only transient *and not irreversible* as was more likely if the fusion was 'too stable' – in which case we would merely produce inactive, "functionless wonders" -- the FBDs would have to be fused through regions that are either inherently flexible (as indeed the C-terminal region of SK is known to be) or, better, through pre-designed, short regions of amino acid residues of *appropriate* flexibility so as to display suitable propensity for plasmin-mediated scission so that the SK region is "liberated" from the hindering FBDs , albeit after an initial hiatus, to initiate native-like PG activation. It is obvious that neither a very decreased flexibility (i.e. highly rigid) or extremely flexible structure would suit the intended aim, since the former, being resistant to proteolysis would tend to produce an inactive fusion, whilst the latter would be activated almost immediately after exposure to even very small concentrations of plasmin. Thus, our designs are tailored to exploit the following factors and their judicious combinations to achieve this objective.

Gyan Sahni

It needs to be recognized here that the active, physiologically existent/relevant form of SK is the SK-PG complex (since SK rapidly forms a 1:1 complex with PG, present in the circulation as soon as it is injected), which *already* contains five kringle domains (present in the PG portion of the complex); further enhancement byincorporating *additional* kringle domains into the SK is unlikely to cause any further benefits to the SK-PG complex *in terms of fibrin affinity, that is of relevance to the 'problem' at hand, namely how* ***to localize, or limit, PG activation near the clot to be dissolved, and not throughout the circulatory system***. Despite the five kringles in the SK-PG complex and its resultant affinity for fibrin that the kringle domains confer, its PG activation remains systemic i.e. it begins to activate PG *throughout* the system as soon as it is injected. It is particularly worth noting in this context that Malke et al. have introduced additional Kringles at the N-terminal end of SK in an effort to improve SK's fibrin affinity but have not demonstrated any increase in this property in either the resultant hybrid or its complex with PG, which is quite surprising in view of the fact that this is a primary aim and objective of their invention. Neither have any alteration in the PG activation kinetics/time-course that might offer localized PG activation at the site of the clot been demonstrated. On the other hand, in the present application, the inventors have incorporated an *altogether different type of fibrin binding domain/s* (called "finger" domains) whose structure and functional properties are distinct from that of kringle domains. Hence, when fused at the N-terminal end, or the C-terminal end through flexible linkers, or both ends simultaneously, the resultant fusions are initially inactive even in the presence of PG (unlike normal SK-PG) but get activated in the presence of plasmin (an active protease that is present in the fibrin clot and normally absent in the circulation), thus giving rise to a time-delayed, plasmin-activable and localized clot dissolution effect.

If the initially delayed kinetics were indeed an intrinsic or inherent property of the fusion/conjugation, a change in the specific activity and/or rate of PG activation would have been expected to occur. **Indeed, we have experimentally observed, like Malke et al, that the fusion of kringle domains at the N-terminus does not confer such a delayed effect, in direct contrast to the fusion of finger FBDs.**

Such an altered attribute has not been disclosed in any of the cited arts, pointing to the non-obviousness of the designs revealed in the instant application to effect a time lag in PG activation, specifically due to a plasmin-dependent switch, by the genetically designed plasminogen activator.

The Examiner has cited Brown et al (Table 6) that the average activity of their conjugate is 38-50% and thus their data establishes low activity at early time-points. **However, we have closely examined that same data and reached the opposite conclusion.** The Table 6 (or for that matter, any data in Brown) only shows the specific activity of the conjugate as a function of different units/ml, i.e, **it only establishes the dose-dependence of activity and is in no way indicative of a lag, delay or altered**

kinetics of PG activation. Indeed, under Table 7 they show a closely similar compromise in the activity of urokinase upon conjugation, indicating that the cross-linking reaction, in this case also, leads to a similar compromise in the bio-activity of urokinase as well.

It would be highly inappropriate, therefore, to conclude from such data that merely making a conjugate (that too heterogenous via chemical linkages) *automatically* allows the generation of the coveted property of time-delayed, plasmin-dependent activation; what the data merely establishes is that the intrinsic activity is compromised in average extent, without having any bearing on the alteration of its kinetics or time-course of manifestation. It is relevant also to state here very unequivocally that the type of covalent bonds engendered by Brown et al's chemical procedure are not amenable to cleavage by plasmin, a natural enzyme that recognizes alpha-amino peptide bonds only.

Similarly, Malke also only say that the resultant conjugates are in possession of SK activity, which is certainly neither here nor there with respect to the kinetics of the activity. **Is it then fair to conclude that any conjugate will show the new and unique property that we are showing, and which clearly has advantageous clinical and therapeutic effects?**

We recognize that the Examiner objection is an objection of obviousness, and we have addressed this objection of obviousness adequately earlier. Yet, we would respectfully submit that there is no inspiration or clue from the each document to seek support for other documents or other areas of knowledge. Each document is stand-alone and there is no logical link between one document to another document. In short, both fall in different directions and the present invention provides yet another direction, which has no bearing on the citations. They are individual patents and there is no motivation to continue. Whereas, the instant invention is made with a progressive approach and not with hindsight.

The Examiner must appreciate that the cited arts are of years 1990 and 1992. We have put several years of research to come out with the invention of the instant application. Had it been obvious for a person skilled in the art, then, would not the much-awaited instant work come out long back? The area of invention is a very 'hot' area of research. This is so because millions of people die from heart attacks and other related disease conditions, and the current thrombolytic drugs, including streptokinase, have severe side-effects emanating from their lack of clot-specific (i.e. systemic) plasminogen activation mode of action. Hence, an improved thrombolytic with a time-delayed, target-activable mode of action as described in the instant invention can be of great value. The instant work is a major breakthrough in the field. A person skilled in the art would immediately realize the significance of the instant work.

Had it been obvious, the invention would have taken place immediately after the cited arts. There are several research groups in various parts of the world that are active in this area of research. Had it been so obvious, they would not have waited for 12-13 years! This can be further substantiated by the fact that, our + the behaviour of the product one actually conducts the experiments, the person cannot be sure about achieving the desired result. The inventors have conducted multiple experiments of varying nature. It is only after several years of hard work involving much human involvement and inventive skills that the inventors have been able to achieve the desired results.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title XVIII of the United States Code and that willful false statements may jeopardize the validity of this Application for Patent or any patent issuing thereon.

Dated: 28/11/2003

Place: Chandigarh, INDIA

GIRISH SAHNI